Changes in carotid plaque echomorphology with time since a neurologic event

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Purpose: **Symptomatic carotid plaques are characterized by reduced fibrous tissue content, increased lipid content, intraplaque hemorrhage, and cap rupture. This confers an increased stroke risk. Plaque remodelling reduces this risk, however, and this study has evaluated differences in echomorphology at varying times after a neurologic event.**
Methods: **Gray scale medians (GSM ± interquartile ranges) were measured using the best single longitudinal (SLV) and multiple cross-sectional views (MCSV; transverse views, 5-mm intervals throughout plaque) on B-mode ultrasound images of 61 carotid plaques (70% to 99%) causing symptoms ≤30 (n = 20), 31 to 90 (n = 10), 91 to 180 (n = 16), or >180 days (n = 15). The results were compared with those in 47 asymptomatic plaques. Plaque echolucency (SLV-GSM, $MCSV^{min}$-GSM [cross-sectional image with lowest GSM]) and heterogeneity ($MCSV^{max-min}$-GSM [highest minus lowest GSM of cross-sectional views]) were determined.**
Results: **In symptomatic plaques, echolucency was maximal ≤30 days of the presenting neurologic event (SLV-GSM, $P = .009$; $MCSV^{min}$-GSM, $P = .004$). Although this diminished between 31 to 90 days, MCSV measurements in particular suggested increased echolucency ($P = .042$ at >180 days) and continuing heterogeneity ($P = .01$ at 91 to 180 days) beyond that time.**
Conclusions: **Plaque echolucency was maximal ≤30 days of a neurologic event but diminished after 1 to 3 months, suggesting remodelling of unstable plaques. Continued features of increased echolucency and heterogeneity >91 days, however, suggests an increased stroke risk in these patients compared with that of the general population. (J Vasc Surg 2007;45:367-72.)**

Clinical Relevance: **This cross-sectional study has demonstrated interesting differences in gray scale median plaque echomorphology with time after the initial neurologic symptom in patients with symptomatic carotid disease. The results raise some important questions with respect to identifying currently asymptomatic patients who might be at greatest risk of a neurologic event and add fuel to the current debate relating to the relative benefits of either carotid endarterectomy or carotid angioplasty and stenting in patients with recent symptoms.**

After a transient ischemic attack, the risk of stroke from a recently symptomatic carotid plaque is maximal immediately, reducing by half after 1 year, and returning to baseline 2 to 3 years after the initial symptom.[1-3] Thus, atheromatous plaques are dynamic structures undergoing continuous remodelling. Histologic studies of excised carotid atherectomy specimens have shown that morphologic features, including a large lipid or necrotic core,[4] particularly when located close to the luminal surface[5]; fibrous cap disruption,[6] intraplaque hemorrhage,[7,8] and surface ulceration,[9] occur more frequently in recently symptomatic plaques.

The morphologic changes associated with plaque instability have been assessed using single longitudinal view (SLV) B-mode ultrasound imaging.[10,11] Previous work from our unit, however, has suggested that computer-assisted multiple cross-sectional view echomorphology (MCSV) may be superior to SLV imaging in identifying these changes.[12]

The natural history of plaque remodelling after a neurologic event remains unknown. Although both the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) used a cutoff of 180 days since symptoms as the therapeutic window for carotid endarterectomy, this was a somewhat arbitrary decision. Indeed, subanalysis from NASCET suggests continued benefit to surgery in subgroups of patients beyond this time period.[13] Thus, the aim of this study was to assess plaque echomorphology for all 70% to 99% carotid stenoses in patients undergoing carotid endarterectomy in our unit to evaluate differences in echolucency and heterogeneity at varying times after the presenting neurologic event.

METHODS

A total of 108 consecutive carotid bifurcation plaques causing 70% to 99% stenosis were studied in 94 patients (60 men, 34 women) referred for consideration of carotid endarterectomy. Informed consent was obtained, and the study was approved by the Ethics Committee of the Leeds Teaching Hospitals NHS Trust.

A detailed neurologic history and examination were recorded, with symptoms classified as amaurosis fugax,

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Competition of interest: none.
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0741-5214/$32.00

doi:10.1016/j.jvs.2006.09.048

defined as sudden onset of partial or complete uniocular visual loss lasting <1 hour; transient ischemic attack (TIA), defined as sudden focal neurologic deficit lasting <24 hours with no other apparent cause; or stroke, defined similarly to TIA but with symptoms lasting >24 hours. Risk factors for vascular disease and medications were documented.

Cerebral hemorrhage and lacunar infarcts were excluded in patients with stroke using cerebral computed tomography (CT) imaging. Also excluded were patients with potential cardioembolic sources for symptoms, such as concomitant cardiac arrhythmia on electrocardiogram or 24 hour Holter monitoring; or atrial thrombus or septal defect on echocardiography. Twelve plaques (6 symptomatic, 6 asymptomatic) were excluded because acoustic shadowing resulted in inadequate B-mode information.

Ultrasound protocol. The percentage of carotid stenosis was determined using duplex criteria for detecting >70% stenoses, validated within our unit, including internal carotid artery (ICA) peak systolic velocity (PSV-ICA >180 cm/s), end-diastolic velocity (EDV-ICA >80 cm/s), and ratio of peak systolic velocity in the ICA and common carotid artery (CCA) [PSV-ICA/CCA >4).[14] A subgroup with 80% to 99% stenosis were also identified (PSV-ICA >250 cm/s; EDV-ICA >100 cm/s).

Gray scale median (GSM) assessment of each plaque was performed using a previously described method.[12] Briefly, patients were scanned by one of two ultrasonographers (blinded to the clinical details) using a high-resolution scanner (Acuson 128 XP10, Siemens, Munich, Germany) and a 5-MHz to 7-MHz multifrequency linear array probe. B-mode settings were fixed throughout the study. The most informative SLV (image with maximum plaque area) of the plaque was obtained using color duplex and the image "frozen."

To determine plaque GSM by the technique of multiple cross-sectional imaging, the carotid bifurcation was located with an axial sweep of the neck, and transverse color flow images were obtained at 5-mm intervals from this point throughout the length of the plaque for a total of five to eight multiple cross-sectional views (MCSV) per plaque. After freezing each color image, the color-off facility of the scanner was used to obtain the gray scale image of each view. These images were digitized in bitmap format by a commercially available video grabber (Matrox Marvel G400 AGP, Dorval, Montréal, Canada) and downloaded to a computer.

Images were normalized with computer software (MATLAB 5.3, The MathWorks, Natick, Mass), using two reference points (blood and adventitia) to a set gray scale from 0 (black) to 255 (white). The GSM for each image was then determined. Although the SLV-GSM provides a single, selected measure of global plaque echolucency, MCSV analysis allows identification of the transverse image with the lowest GSM (MCSV-GSM^{min}) reflecting maximal focal echolucency. Further, the difference between maximum and minimum GSM (MCSV-GSM$^{max-min}$) in the transverse images assesses plaque heterogeneity, which cannot be quantified with SLV imaging. We have previously published satisfactory correlations for intraobserver and interobserver error for this technique.[12]

Table I. Demographic factors and neurologic symptoms in study patients

	N	*Sex (M/F)*	*Age (years) median (range)*	*Symptoms**
Symptomatic				
<30 days	20	12:8	66.5 (46-83)	16:4
31-90 days	10	6:4	72.5 (54-87)	7:3
91-180 days	16	12:4	74.5 (60-80)	8:8
>180 days	15	13:2	69 (52-86)	10:5
Asymptomatic	43	24:19	72 (48-86)	

*Hemispheric/amaurosis fugax ratio.

Table II. Ipsilateral percentage of internal carotid artery stenosis in study patients

		Stenosis		
	Patients (n)	*70%-79% n (%)*	*80%-89% n (%)*	*90%-99% n (%)*
Symptoms				
<30 days	20	6 (30)	6 (30)	8 (40)
31-90 days	10	3 (30)	4 (40)	3 (30)
91-180 days	16	5 (31)	8 (50)	3 (19)
>180 days	15	4 (27)	7 (47)	4 (26)
Asymptomatic	47	12 (26)	18 (38)	17 (36)
*P**		.99	.77	.66

*Differences between all groups; χ^2.

Patients were divided into five groups for analysis according the most recent neurologic event: symptoms ≤30 days; symptoms from 31 to 90 days; symptoms from 91 to 180 days; symptoms >180 days previously; and asymptomatic.

Histology protocol. Endarterectomy was performed using a modified technique to yield an intact plaque,[14] under either local or general anesthesia. Transverse sections were made at 4-mm intervals proximal and distal to the carotid bifurcation. They were placed in 4% paraformaldehyde solution for 24 hours and then decalcified in ethylenediamine tetraacetic acid (EDTA) for 2 weeks before being embedded in paraffin. Sections (5 μm) from each paraffin block were stained with hematoxylin and eosin, van Gieson, and Sirius red, and reported by a senior cardiovascular pathologist blinded to clinical details.

Plaques with rupture or cap thinning were designated unstable. Plaque rupture was defined as disruption of the cap with direct communication between the lumen and lipid core. Cap thinning was defined by the absence of collagen or elastin tissue within the entire cap on at least one section but usually on several sections throughout the plaque. Plaques without either of these features were designated stable.

Statistical analysis. The χ^2 test was used to determine differences in proportions. The Kruskal-Wallis test compared age between groups. The one-sample Kolmogorov

Table III. Risk factors for vascular disease in study patients

	Patients (n)	*Hypertension n (%)*	*Diabetes mellitus n (%)*	*Hyperlipidemia n (%)*	*Current smoker n (%)*
Symptoms					
<30 days	20	13 (65)	3 (15)	15 (75)	11 (55)
31-90 days	10	6 (60)	3 (30)	7 (70)	1 (10)
91-180 days	16	11 (69)	1 (6)	13 (81)	5 (31)
>180 days	15	11 (73)	2 (13)	9 (60)	5 (33)
Asymptomatic	43	29 (67)	7 (16)	34 (79)	30 (70)
*P**	0.78	0.97	0.69	0.01	

*Difference between all groups; χ^2.

Table IV. Median value for gray scale median and interquartile range for each subgroup

	N	*SLV-GSM*	P*	*MCSV-GSM^{min}*	P*	*MCSV-GSM$^{max-min}$*	P*
Symptoms							
<30 days	20	13.1 (6.4-35.3)	.009	0.95 (0.0-8.8)	.004	30.2 (15.5-40.3)	.08
31-90 days	10	22.0 (10.5-45.0)	.43	6.5 (1.5-12.0)	.17	28.0 (13.3-60.3)	.20
91-180 days	16	33.0 (10.0-48.0)	.77	7.0 (2.0-14.5)	.09	32.0 (26.0-48.0)	.01
>180 days	15	20.0 (3.0-39.0)	.07	5.3 (0.0-15.0)	.042	28.0 (15.6-42.0)	.15
Asymptomatic	43	32.5 (19.0-56.3)	—	13.4 (1.5-28.3)	—	16.5 (8.0-30.8)	—

SLV, Single longitudinal view; *GSM,* gray scale median; *MCSV,* multiple cross-sectional views; *GSM^{min},* lowest gray scale median; *GSM$^{max-min}$,* highest minus lowest gray scale median of cross-sectional views.
**P* vs asymptomatic; Mann-Whitney.

test determined that GSM data was nonparametric, and thus the Mann-Whitney *U* test was used for comparative analysis. $P < .05$ was considered significant. Statistical tests were performed using SPSS 11.0 (SPSS Inc, Chicago, Ill) computer software.

RESULTS

Of 108 consecutive 70% to 99% carotid stenoses, 61 had caused symptoms ≤30 (n = 20), 31 to 90 (n = 10), 91to 180 (n = 16) or >180 days (n = 15) earlier. A further 47 asymptomatic plaques were also identified, including 24 asymptomatic bruits identified before coronary artery bypass grafting, seven bilateral; 11 contralateral to symptomatic occlusion, and 12 contralateral to symptomatic high-grade stenoses.

There were no demographic differences among the symptomatic groups, and the ratio of hemispheric TIA and stoke to amaurosis fugax was similar in each of these (Table I). Similarly, no difference was found in the percentage of ipsilateral stenosis between groups ($P = .69$; Table II). There were more current smokers amongst the asymptomatic patients ($P = .01$; Table III).

Echomorphology results. The median GSM ± interquartile range for each group is summarized in Table IV. Global plaque echolucency (SLV-GSM) was maximal in the most recently symptomatic plaques, with a stepwise return to near asymptomatic levels by 91 to 180 days, suggesting remodelling of the plaque. There was, however, a trend towards increasing echolucency in plaques remaining asymptomatic for >180 days (Fig 1). This pattern was accentuated when assessing focal plaque echolucency (MCSV-GSM^{min}), with GSM never returning to asymptomatic values (Fig 2). Plaque heterogeneity was increased in all symptomatic plaque groups vs asymptomatic plaques, reaching significance only in the 91 to 180 day group, with no clear pattern suggesting remodelling with this marker of plaque instability (Fig 3).

Relationship of plaque echomorphology with histology. Histologic data were available from 65 patients (plaques) after both echomorphologic assessment and carotid endarterectomy, of which 28 were designated unstable (16 rupture, 12 cap thinning) and 37 stable. The median SLV-GSM was significantly lower in unstable plaques vs stable plaques (15 [IQR, 4 to 31] vs 32 [IRQ, 17 to 48]; $P = .01$; Fig 4). A similar trend was seen for MCSV-GSM^{min} (2 [IQR, 0 to 9] vs 11 [IQR, 4 to 16]; $P = .008$; Fig 5).

DISCUSSION

This cohort study is, to our knowledge, the first to assess differences in carotid plaque echomorphology in relation to the time since a neurologic event. We have demonstrated changes in both global and focal plaque echolucency within the first 180-day period after the presenting neurologic symptom, which would be consistent with plaque remodelling. Pathophysiologically, this is likely to represent resorption of intraplaque hemorrhage, an increase in plaque fibrous content, and a reduction in the lipid/necrotic core. By contrast, no significant change was noted in overall plaque heterogeneity during this period.

Surprisingly, plaques that were assessed >180 days after the presenting symptom demonstrated features that would suggest that they might have become less stable over time. This may explain the ongoing risk of a neurologic

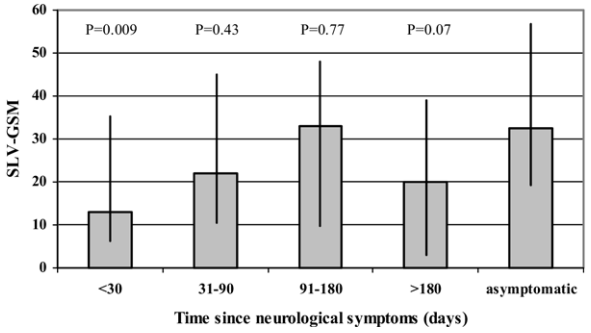

Fig 1. Comparison of plaque SLV-GSM with time since a neurologic event (*P* vs asymptomatic; Mann-Whitney test). *SLV,* Single longitudinal view; *GSM,* gray scale median.

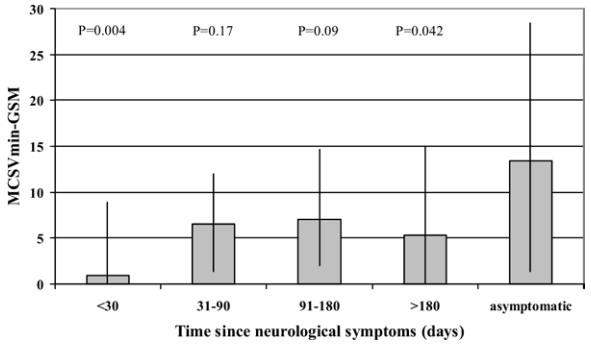

Fig 2. Comparison of plaque MCSV-GSM^{min} with time since a neurologic event (*P* vs asymptomatic; Mann-Whitney test) *MCSV,* multiple cross-sectional views; *GSM^{min},* lowest gray scale median.

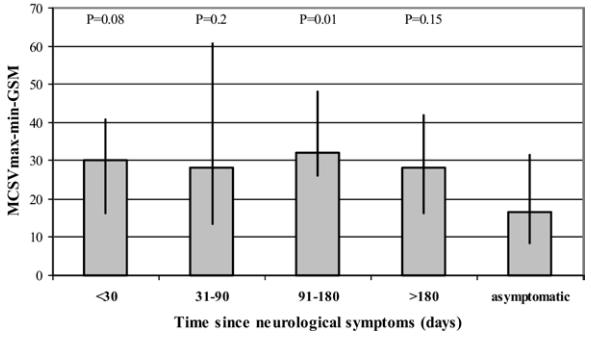

Fig 3. Comparison of plaque heterogeneity (MCSV-GSM$^{max-min}$) with time since a neurological event (*P* versus asymptomatic; Mann-Whitney). *MCSV,* Multiple cross-sectional views; *GSM$^{max-min}$,* highest minus lowest gray scale median of cross-sectional views.

event >180 days in these patients. This is consistent with the findings of previous clinical studies that have confirmed that the risk of stroke in such patients remains elevated for up to 3 years.[1,2] No differences were found in patient demographics, degree of stenosis or the type of neurologic symptoms between symptomatic groups to account for these findings, although such a conclusion must remain guarded owing to the small patient numbers in each group.

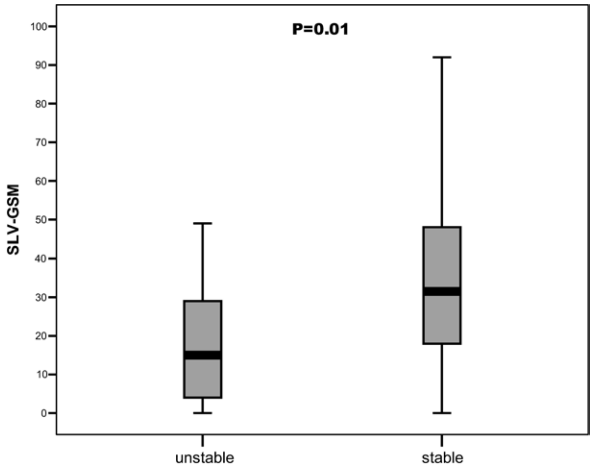

Fig 4. Comparison of plaque SLV-GSM in unstable and stable plaques on histology (*P*, Mann-Whitney). *SLV,* Single longitudinal view; *GSM,* gray scale median. Data presented with mean, interquartile range ±95% interval.

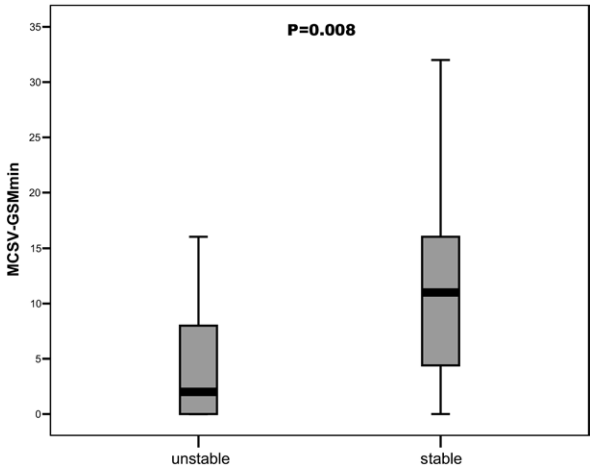

Fig 5. Comparison of plaque MCSV-GSM^{min} in unstable and stable plaques on histology (*P*, Mann-Whitney). Data presented with mean, interquartile range ±95% interval. *MCSV,* multiple cross-sectional views; *GSM^{min},* lowest gray scale median.

Histologic differences between symptomatic and asymptomatic plaques have been described previously, although studies report conflicting results. Feeley et al[4] examined pathologic differences between 44 symptomatic and eight asymptomatic plaques, demonstrating a reduction in collagen/fibrous tissue in those causing symptoms (66% vs 88% of plaque volume). They were unable to identify a relationship between plaque structure and either the time since or the number of neurologic events, leading them to conclude that symptomatic plaques did not heal.[4]

Conversely, in a cross-sectional study of 270 plaques, the European Carotid Plaque Study reported a reduction in the "soft tissue" content of plaques examined >5 months after symptoms.[15] Although this would be consistent with plaque remodelling, it might be that plaques with a lower soft-tissue component were less likely to cause further symptoms between the first neurologic episode and carotid endarterectomy.

In a recent study assessing histology of 526 symptomatic carotid plaques in relation to nature and timing of ischemic symptoms, plaques causing stroke were most unstable immediately after the neurologic event, with the prevalence of plaque rupture and instability falling to plateau levels at approximately 90 to 100 days. Interestingly, cap rupture, inflammation, and instability in plaques causing TIAs was a less common feature immediately after symptoms, and the prevalence did not change with time since the neurologic event.[16] These findings of possible histologic remodelling in plaques causing recent stroke would be in keeping with the echomorphologic changes seen within the first 180 days after a neurologic event in this study.

Echomorphologic assessment of carotid plaques was first described in 1983, demonstrating the association between plaque heterogeneity, intraplaque hemorrhage, and recent symptoms.[17] A more detailed classification of SLV plaque echomorphology was proposed in 1989[18]; however, the subjectivity of this technique, associated with changes in plaque echomorphology with both symptomatology and degree of stenosis,[19,20] has led to conflicting results in the literature.

The introduction of computer-assisted echomorphologic assessment,[21] particularly when combined with gray scale normalization,[22] has led to acceptable reproducibility in both single longitudinal[23] and multiple cross-sectional[12] views. Further, differences in the B-mode ultrasound GSM of various tissue components have been demonstrated[24,25] and associated with specific histologic features in carotid plaques.[24-26]

It must be emphasized that this is a cohort study with a relatively small number of plaques in each group. Despite this, the results are of considerable interest. Maximal differences in plaque echomorphology between asymptomatic and symptomatic plaques occur in the first 30 days after a neurologic event and persist to a lesser degree for up to 90 days. The assumption that such differences reflect plaque instability would be entirely consistent with epidemiologic evidence that demonstrates a higher risk of a second neurologic event closely following the presenting symptom.[3] It further supports the findings of the Imaging in Carotid Angioplasty and Risk of Stroke study, which reported that plaques with a low SLV-GSM (<25) are more likely to have an adverse outcome from carotid angioplasty and stenting,[27] consistent with an increased risk of embolization from unstable plaques.

The correlation between GSM and plaque histology in this study, combined with data from two large histologic studies,[15,16] supports the concept of plaque remodelling to a more stable configuration with increasing time after an ischemic neurologic event. No longitudinal echomorphologic data are available to confirm these findings, however, and this type of study would now be considered unethical.

Alternatively, it is possible that plaques with a more stable configuration are less likely to cause recurrent symptoms, which might lead to a longer time interval between the initial event and ultrasound assessment. There was no evidence that this was the case in the current study, and the finding of maximal instability immediately after an event with a stepwise return to a more stable configuration over the following 90 days would favor true plaque stabilization.

A final, important research question to address is the timescale of changes in asymptomatic plaque echomorphology before a neurologic event in those that become symptomatic. The Asymptomatic Carotid Surgery Trial indicates that some 11% of asymptomatic plaques become symptomatic by the end of a 5-year period.[28] A longitudinal study of plaque echomorphology, particularly MCSV-GSM^{min} in patients with an asymptomatic ≥70% stenosis, would be of considerable interest.

CONCLUSION

This cohort study has demonstrated interesting differences in GSM plaque echomorphology with time after the most recent neurologic symptom in patients with symptomatic carotid disease. The results raise some important questions with respect to identifying currently asymptomatic patients who might be at greatest risk of a TIA or stroke and add to the debate concerning the relative risk/benefit of carotid endarterectomy or CAS in recently symptomatic patients.

AUTHOR CONTRIBUTIONS

Conception and design: DR, MW, MG
Analysis and interpretation: DR, MW
Data collection: DR, MW, MG
Writing the article: DR, MG
Critical revision of the article: DR, MW, MG
Final approval of the article: DR, MW, MG
Statistical analysis: DR
Obtained funding: Not applicable
Overall responsibility: MG

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Submitted Aug 1, 2006, accepted Sep 19, 2006.